

CANCER

Study Suggests New Way to Gauge Prostate Cancer Risk

Prostate cancer is many men's worst fear. The most common cancer to strike non-smoking men, it has felled a long list of public figures, including rock star Frank Zappa and 1960s guru Timothy Leary. Other aging baby boomers are now demanding blood tests to see if their prostate specific antigen (PSA) levels are high, a sign that cancer may already lurk in their prostates, and many men can rattle off their PSA levels with as much familiarity as their cholesterol counts.

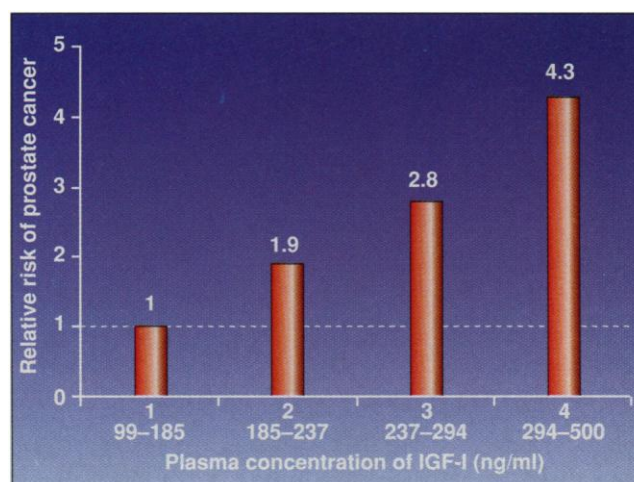
The PSA test detects the signal of cancers already under way, but it can't identify men at high risk of getting prostate cancer *before* they develop the disease, in the way cholesterol serves as a heads-up for heart disease. But now, a team of researchers from Harvard and McGill universities has come up with a molecule that may provide just such an early warning. They report on page 563 of this issue that men whose blood contained high levels of a protein called insulin-like growth factor-I (IGF-I) were four times more likely to develop prostate cancer than were men with the lowest IGF levels. "Of all the associations [with prostate cancer] we have looked at, this is one of the strongest," says Ann Hsing, an epidemiologist who studies prostate cancer at the National Cancer Institute (NCI). Assuming that these results are confirmed, they "have implications for prevention, detection, and treatment," says NCI cancer epidemiologist Joseph Fraumeni. An IGF-I test might be used to identify high-risk men who need close monitoring or to recognize potentially aggressive tumors while they're still small, and it could also lead to ways of lowering men's risk.

The authors stress that such potential applications are still years away. "We are not suggesting that this report allows us to determine clinical practice," says senior author Michael Pollak, a clinical oncologist at McGill University in Montreal, "but there are lines of investigation that it opens up."

Any new approaches that might help manage this slippery disease would be welcome. Just last week, the American Cancer Society called for increased research and education on prostate cancer, especially for African-American men, who are twice as likely to develop the disease as whites are. As awareness grows, experts are struggling with thorny issues of whom to screen and whom to treat,

because some argue that mass screening is not cost-effective. They note that the PSA test may help spot some cancers early, but because many cancers don't advance to life-threatening disease even if left untreated, the test probably leads to many unnecessary surgeries.

Seeking a new angle on these screening and treatment dilemmas, the researchers turned to IGF-I. They already knew from laboratory studies that the molecule is a powerful growth factor that stimulates the growth of both cancerous and normal prostate cells. To see if it was linked to disease in people, the team studied nearly 15,000 men enrolled in the Physicians' Health Study at Harvard. Those men gave blood



Estimating the odds. Men with the highest IGF-I levels have four times the risk of prostate cancer of men with the lowest levels.

samples in 1982 and then were monitored for a wide variety of diseases and conditions. By 1992, 520 had been diagnosed with prostate cancer. Of these, 152 had blood samples large enough to be assayed for IGF-I; Harvard School of Public Health graduate student June Chan compared these 1982 IGF-I levels to those of 152 men without cancer who were matched for age and other factors. "The basic question we addressed," says team member Edward Giovannucci of Harvard Medical School, "is if you look at the normal range of [IGF-I] variation in men, [does] having relatively high levels render a man at higher risk for prostate cancer?" The answer was a resounding yes. When the men were sorted by their 1982 IGF-I levels, the 25% who fell at the high end of the IGF-I range were 4.3 times more likely to have developed prostate cancer than were the men at the low end.

In most cases, it appears that the men didn't have cancer in 1982, because their PSA levels were normal and their cancer wasn't diagnosed until an average of 7 years later. That means "IGF is telling you something before the disease occurs," says Giovannucci, "just like if you have a cholesterol [level] of 300, you are more worried [about heart disease] than if you have a [level] of 180." Drugs can lower IGF-I levels, so if the molecule does indeed help cause cancer rather than merely being associated with it, then it might be possible to lower a man's risk of prostate cancer.

The team's findings also offer some hope that IGF levels may help physicians determine which tumors are most likely to grow large enough to be invasive and life-threatening. The researchers tested all the 1982 blood samples for PSA and found 60 men with high levels, suggesting that they already had undetected early-stage cancer. As in the group as a whole, these men showed a range of IGF-I levels, but those with the highest levels were four times more likely to develop full-blown cancer than were those with low levels, suggesting that high IGF-I increases the chance that prostate cancer will grow.

Because the numbers are small, that finding is far less certain than the paper's main conclusions, says Pollak. But it has already sparked interest in further studies. A Stanford research team has spent years sectioning surgically removed prostates to define tumor traits that predict aggressive disease, notes Donna Peehl, a tumor biologist at Stanford Medical School who studies prostate cancer. She's eager to see whether IGF-I levels correlate with those traits, and so might be an indicator of a tumor's aggressiveness.

Indeed, the biggest effect of this paper may be to stir up new research.

"A paper like this, which is so provocative, raises a whole spectrum of questions," says cancer epidemiologist David Schottenfeld of the University of Michigan School of Public Health. For example, the men in the Physicians' Health Study were overwhelmingly white, and he'd like to examine IGF-I levels in African-American men, given their higher risk of prostate cancer. And because IGF is a growth factor with influence on many tissue types, the researchers are also looking at other cancers. In as-yet-unpublished work, Pollak and colleagues have found an equally strong association between IGF-I levels and the risk of breast cancer, and they are now seeking links to colon cancer. This next round of research may help determine whether people will someday watch their IGF-I levels as carefully as they plot PSA and cholesterol today.

—Marcia Barinaga